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High Yield Synthesis of the Parent C-Unsubstituted Calix[4]resorcinarene Octamethyl Ether

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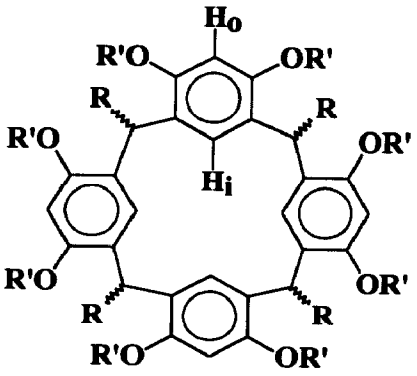
Abstract: Treatment of 2,4-dimethoxybenzyl alcohol with trifluoroacetic acid (TFA, 5% in $CHCl_3$) affords, in almost quantitative yield calix[4]resorcinarene octamethyl ether, which on demethylation and acetylation yields the derived octa-acetate.

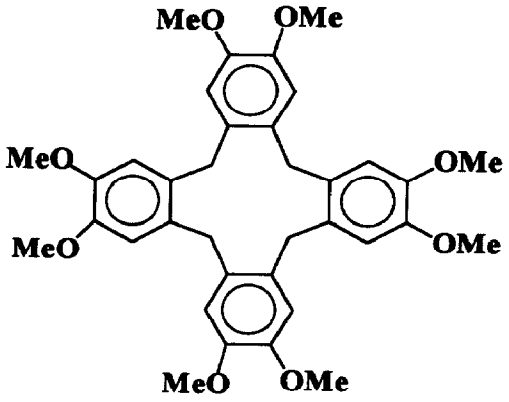
The preparation of C-alkylated calix[4]resorcinarenes by acid catalyzed condensation of resorcinol with a variety of aldehydes has been known for more than one hundred years.[1,2,3] In 1940, Niederl and Vogel[4] reported the synthesis of C-methyl calix[4]resorcinarene **2** by the H_2SO_4 catalyzed condensation of resorcinol with acetaldehyde. C-Arylated calix[4]resorcinarenes were similarly prepared from aryl aldehydes and resorcinol.[5] Högberg[6] isolated two of the four possible stereoisomers of C-phenyl calix[4]resorcinarene **5** from the condensation of resorcinol and benzaldehyde. He subsequently proved the presence of two stereoisomers of **2** in the product mixture of the condensation of acetaldehyde and resorcinol.[7] Unlike the reaction with higher aldehyde homologues, polymer, rather than the C-unalkylated calixarene tetramer, is formed when formaldehyde is treated with resorcinol (or phenol) under similar conditions.[8] The parent calix[4]resorcinarene **1** is thus unavailable by this method and to our knowledge is still unknown.

We have recently reported on the use of trifluoroacetic acid (TFA) in the catalysis of a number of cyclodimerization[9] and cyclo-oligomerization reactions. For example, veratryl alcohol (3,4-dimethoxybenzyl alcohol) affords cyclotri-, cyclotetra-, cyclopenta- and cyclohexaveratrylene oligomers (**7**, **8**, **9** and **10**) when dehydrated in the presence of TFA[10]. Similarly, cyclotribromoveratrylene **11**, an extractive of *Halopytis pinastroides*, can be easily prepared from 5-bromoveratryl alcohol.[11] Thus, with 3,4-dimethoxybenzyl alcohols, *cycloveratrylenes* are formed by alkylation of the available site *para* to a methoxy group. In contrast, with 2,4-dimethoxybenzyl alcohol, we have found that *resorcinarenes* are produced by alkylation at the site *ortho* and *para* to the ether substituents. This divergence of product structure based on substitution pattern in the starting alcohol is of synthetic interest and offers a convenient method for the preparation of resorcinarenes. Using this methodology, we herein report the first synthesis of the C-unalkylated calix[4]resorcinarene octamethyl ether **3**, further characterized as the octa-acetate derivative **6**.

When 2,4-dimethoxybenzyl alcohol **12**[12] was treated with TFA (5% in $CHCl_3$) at ambient temperature (18 h), a purple solid was obtained on evaporation of the solvent. The presence of a single major component was indicated from the ^1H NMR spectrum of the crude product mixture. This component (**3**) was isolated as an off-white powder in high yield (95%; mp >360 °C) after trituration with boiling acetone. The ^1H NMR spectrum exhibited a methylene, a methoxyl and two aromatic singlets in a ratio of 2:6:1:1 (see Table 1). The absence of the third aromatic proton of the starting alcohol and the presence of symmetry in this product, as evidenced by only six peaks in its ^{13}C NMR spectrum (see Table 2), suggested a cyclic structure. The tetrameric nature of the oligomer was proven by mass spectral analysis (HRMS, M/e 600.2704; calc. for $C_{36}H_{40}O_8$, 600.2723)[13,14] and corresponds to the assigned structure **3**, calix[4]resorcinarene octamethyl ether.[15]



1 R=R'=H
2 R=CH_3; R'=H
3 R=H; R'=CH_3
4 R=R'=CH_3
5 R=Φ; R'=H
6 R=H; R'=Ac



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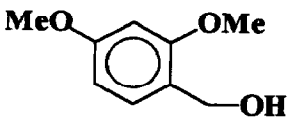
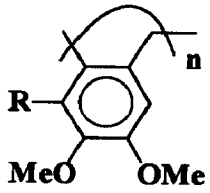


12



7 R=H; n=3
9 R=H; n=5
10 R=H; n=6
11 R=Br; n=3

Table 1. The ^{1}H NMR chemical shifts (δ_{ppm} from TMS) of calix[4]resorcinarenes **3** and **6** in $CDCl_3$ (300 MHz).[a,b]

	ArH_i	ArH_o	CH_2	OCH_3	O(C=O)CH_3
3	6.42 s	6.18 s	3.69 s	3.78 s	
6	6.90 s	6.53 s	3.62 s		2.21 s

a) Spectra taken at ambient temperature.
b) H_i = inner aromatic proton; H_o = outer aromatic proton.

Table 2. The ^{13}C NMR chemical shifts (δ_{ppm} from TMS) of calix[4]resorcinarenes **3** and **6** in $CDCl_3$ (75 MHz).[a,b]

	Ar*C*OMe	Ar*C*OAc	Ar*C*CH_2	ArC_i	ArC_o	CH_2	OCH_3	O(C=O)CH_3	*C*=O
3	156.47		130.72	120.59	95.12	28.26	55.82		
6		147.34	131.43	128.93	116.56	29.39		20.68	168.68

a) Ambient temperature. b) ArC_i = inner aromatic carbon; ArC_o = outer aromatic carbon.

Calix[4]resorcinarene **3** was converted to its octa-acetate **6** by a standard procedure. Thus, when octamethyl ether **3** was treated with BBr_3 in dry $CHCl_3$ at -78 °C for 24h a brick-red solid was obtained (presumably **1**) whose ^{1}H NMR spectrum indicated the absence of the methoxyl peak (3.78 ppm) of **3**. When this product, without further purification, was treated with acetic anhydride in pyridine, the calix[4]resorcinarene octa-acetate **6** (mp 296-297 °C)[16] was obtained as an off-white powder after trituration with boiling ethanol (25% from **3**). The ^{1}H and ^{13}C NMR spectra of **6** are summarized in Tables 1 and 2.

The spectroscopic evidence supports either a rigid saddle conformation for calix[4]resorcinarenes **3** and **6**, or conformational mobility.[17] This is indicated by the equivalency of each methylene proton, the four *inner* aromatic protons and the four *outer* aromatic protons in both **3** and **6**. The data excludes the existence of locked crown, chair or boat conformations in solution.[5,18]

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References and Notes

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1. Gutsche, C. D. *Calixarenes*; Stoddard, J. F., Ed., Monographs in Supramolecular Chemistry, The Royal Society of Chemistry, Cambridge, 1989.

2. (a) Bayer, A. *Ber.* **1882**, *5*, 25, (b) Michael, A. *J. Am. Chem. Soc.* **1883**, *5*, 338.

3. Liebermann, C.; Lindenbaum, S. *Ber.* **1904**, *37*, 2728.

4. Niederl, J.; Vogel, H. J. *J. Am. Chem. Soc.* **1940**, *62*, 2512.

5. Erdtman, H; Högberg, A. G. S.; Abrahamsson, S.; Nilsson, B. *Tetrahedron Lett.* **1968**, 1679.

6. Högberg, A. G. S. *J. Am. Chem. Soc.* **1980**, *102*, 6046.

7. Högberg, A. G. S. *J. Org. Chem.* **1980**, *45*, 4498.

8. (a) Caro, N. *Ber.* **1892**, *25*, 939, (b)Zinke, A.; Zeigler, E. *Ber.* **1944**, *B 77*, 26, (c) *Riegel's Handbook of Industrial Chemistry* Kent, J. A. *Ed.*, Van Nostrand Reinhold Co., New York, *7th* ed., 1974, p. 818, (d) See reference 1, p. 32.

9. Al-Farhan, E.; Keehn, P. M.; Stevenson, R. *J. Chem. Res.* **1992**, *37*, 36.

10. Al-Farhan, E.; Keehn, P. M.; Stevenson, R. *Tetrahedron Lett.* **1992** *33*, 3591.

11. Al-Farhan, E.; Falana, O. M.; Keehn, P. M.; Stevenson, R. *Tetrahedron Lett.* **1992**, *33*, 5885.

12. Alcohol **12** was obtained by borohydride reduction of the corresponding aldehyde. Thus, $NaBH_4$ (0.8 g) was added to 2,4-dimethoxybenzaldehyde in MeOH (150 mL) and the solution stirred for 18 hrs. After quenching with water (50 mL) and concentration of the solvent under reduced pressure the mixture was extracted with benzene. The extract was dried with $MgSO_4$ and the solvent removed under reduced pressure. Alcohol **12** was obtained as an oil (4.3 g, 86%); ^1H NMR ($CDCl_3$): δ 7.16 (d, Ar*H*), 6.46 (s, Ar*H*), 6.44 (d, Ar*H*), 4.60 (s, CH_2), 3.83 (s, OCH_3), 3.80 (s, OCH_3), 2.32 (br s, O*H*).

13. Instrument: MAT 90, EI peak matching.

14. Elemental analysis: **3** Calcd for $C_{36}H_{40}O_8.1/2H_2O$: C, 70.94; H, 6.73. Found: C, 70.79; H, 6.77.

15. Based on the *Beilstein* and *Chemical Abstracts* nomenclature for the known C-methyl analogue **4**, compound **3** would be named, 3,5,10,12,17,19,24,26-octamethoxy[1.1.1.1]methacyclophane or 4,6,10,12,16,18,22, 24-octamethoxypentacyclo[19.3.1.$1^{3,7}$.$1^{9,13}$. $1^{15,19}$]octacosa-1(25),3,5,7(28),9,11,13(27),15, 17,19(26),21,23-dodecaene.

16. Elemental analysis: **6** Calcd for $C_{44}H_{40}O_{16}$: C, 64.08; H, 4.89. Found: C, 63.71; H, 4.88.

17. Within the constraints of limited solubility, there is no marked change in the ^1H NMR spectrum of **3** ($CDCl_3$) from +80 to -50 °C and of **6** ($CDCl_3$) from +100 to -60 °C.

18. White, J. D.; Gesner, B. D. *Tetrahedron Lett.* **1968**, 1591.

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